REMARKS

Claims 4, 15, 25, and 36 have been cancelled. Claims 1, 2, 10, 12, 21, 31, and 47-49 have been amended. Claims 3, 8, 19, 29, and 40 have been withdrawn. Claims 1-3, 5-14, 16-24, 26-35, and 37-57 are now pending in this application. Claims 1-2, 5-7, 9-14, 16-18, 20-24, 26-28, 30-35, 37-39, and 41-57 are before the Examiner. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Election of species

The Examiner's indication of rejoinder for claims directed to DCs of lymphoid origin is acknowledged. Accordingly, claims 3, 8, 19, 29 and 40 remain withdrawn from consideration.

Defective oath

The Office Action states that the oath or declaration is defective because of uninitialed changes in the residence address of Inventor Lespagnard. A substitute Declaration was submitted in parent application no. 09/951,849. A copy of this substitute Declaration is submitted herewith (Attachment A). In accordance with M.P.E.P. 602.05(a), the copy of the substitute Declaration has been labeled with the application number of the present application to avoid incorrect matching with the prior application file.

Objection to the specification

The priority data on the first page of the application has been corrected and updated. Withdrawal of the objection is respectfully requested.

Priority

The Examiner states that due to the broad interpretation of the term "dendritic cells", the instant application is granted the benefit of priority of the '507 application (March 29, 1996), with exception of claims 6, 8, 17, 19, 27, 29, 38, and 40 which are given the priority date of the '502 application (3/27/98).

With this response, Applicants have narrowed the definition for the dendritic cells based on the definition as set forth on page 4, lines 7-8, page 4, lines 11-15 and page 11 lines 23-26 of the present specification, where the DCs are defined as part of the DLC cell population. Also in

the '480 patent application, on for instance page 3, lines 4-12, said definition may be found. Therefore, at least present claims 1-2, 5, 7, 9-16, 18, 20-24, 26, 28, 30-35, 37, 39, and 41-57 may claim the benefit of the priority of the '480 application (March 31, 1995).

Applicants agree that claims 6, 17, 27, and 38 directed to dendritic cells of lymphoid origin claim the benefit of the priority of the '502 application (3/27/98). These claims are active in the application in view of the Examiner's rejoinder of these claims (see paragraph 1 of the Office Action at page 2).

The priority date of claims 3, 8, 19, 29, and 40 is moot as these claims are withdrawn from consideration.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 4, 5, 6, 7, 9, 10, 11, 15, 16, 17, 18, 20, 21, 22, 25, 26, 27, 28, and 29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo, et al. (1994) in view of Sornasse, et al (1992).

The Office Action states that Guo, et al. teach production of hybrids/hybridomas by fusion of a bone marrow-derived antigen presenting B cell and a tumor cell. While Guo, et al. do not teach dendritic cells as fusion partners, the Examiner asserts that it would be obvious to substitute a dendritic cell for the B-cell of Guo, et al. in view of Sornasse, et al. because Sornasse, et al. teach that DCs induce a more vigorous response, including a Th1 response, in vivo.

The claims have been amended to specifically exclude both B-lymphocytes and T-lymphocytes. Support for the amendment is found in the specification at page 11, line 24 and page 51, lines 21-24. The presently claimed invention is clearly non-obvious over Guo, et al. as the B-cells of Guo, et al. are specifically excluded. Furthermore, Sornasse, et al. do not provide sufficient motivation to substitute dendritic cells for the B-cells taught by Guo, et al. In any case, neither Sornasse, et al nor Guo, et al. teach or suggest the importance of isolating DCs from a source rich in DC progenitors such as the recited bone marrow, blood or lymph at a time when the DCs are proliferating and are not yet at a mature stage as claimed.

Applicants position is that one of ordinary skill in the art at the time of the claimed invention would not be motivated to substitute a DC for the B-cell of Guo, et al. based upon the disclosure of Sornasse, et al. There is no teaching or suggestion in either reference that DCs

could be isolated and combined with tumor cells to produce DC/tumor cell hybrids with anti-tumor activity. As discussed in the Moser I Declaration of record in related applications (application nos. 09/951,849 & 09/802,397) and submitted herewith (Attachment B), it was not predictable at the time of the claimed invention that replacing the B-cells of Guo, et al. with DC cells would provide the DC/tumor cell hybrids of the claimed invention because it was known at the time of the claimed invention that fusion of dissimilar cells often resulted in loss of tissue specific traits. Accordingly, one of ordinary skill in the art would not be motivated to combine DCs with tumor cells to obtain DC/tumor cell hybrids. There was no expectation, based upon the cited references, that DC/tumor cell hybrids could be made and administered to produce an anti-tumor response.

The present claims have been amended to specify that the isolation of the DCs is "from bone marrow, lymph or blood", or from dendritic cells prepared "by differentiating in vitro proliferating dendritic cell precursors isolated from bone marrow, lymph or blood". Support for the amendment is found in cancelled claims 4, 15, and 25 and in the specification at page 25, lines 13-25, and Embodiments A-M in the specification at pages 28, line 20 to 30, line 13, for example. Support for proliferating cells is found at page 66, lines 13-14. In particular, Example 12 teaches the a successful hybrid between a bone marrow-derived DC and a tumor cell.

Despite the Examiner's assertions to the contrary, neither Guo, et al nor Sornasse, et al. teach isolation from bone marrow, blood or lymph. Guo, et al. teach isolation of B-cells from spleen (see page 518, col. 1, last paragraph) and Sornasse, et al. teach isolation of DCs from spleen (see pages 15-16, bridging paragraph). As taught by the present application, spleen is disfavored as a DC source in the practice of the claimed method. Although Examples 1-6 of the present application are directed to spleen as a source of DCs for DC/tumor cell hybrids, in fact, these experiments only produced a T-cell/tumor cell hybrid. As taught in the specification at page 66, lines 8-15, "Fusion experiments have been performed using P815 and dendritic cells isolated from spleen. The yield of hybrid clones was very low, as compared to fusions between P815 and bone-marrow derived DC, and none of them displayed phenotypic and functional features of dendritic cells, suggesting that fusion partners should be proliferating cells or dendritic cells at a more immature stage." The present application teaches away from the use of spleen as a source for DCs for hybrids prepared according to the claimed method. Accordingly,

even if one of ordinary skill in the art would have been motivated to substitute the B-cell of Guo, et al. with a DC (and Applicants maintain that the cited references do not provide such motivation), based upon both the disclosures of Guo, et al. and Sornasse, et al., one of ordinary skill in the art would have used spleen as the source of the DCs. As shown by the specification, DCs produced from spleen do not produce very many DC/tumor cell hybrids and do not produce hybrids with an anti-tumor response. Consequently, there was no expectation of success in achieving the invention as claimed by following the teachings of the two cited references.

As discussed in paragraph 9 of the attached Moser II Declaration (Attachment C, also submitted in related application nos. 09/951,849 & 09/802,397), spleen and lymph nodes contain a high proportion of differentiated DCs. These make poor fusion partners. This was not known by others at the time of the claimed invention but was discovered by the inventors of the present application and is clearly shown in the specification. Examples 1-6 of the present specification also demonstrate that DC/tumor cell hybrids could not be produced using spleen as the DC source.

As argued previously, while DCs may be present in spleen, it is not feasible to produce DC/tumor cell hybrids starting from spleen cells. This is illustrated in the present application (see examples 1-6 of the present application) and Guo et al. (1994). Both confirm that, when using spleen cells, B-cell/tumor cell and T-cell/tumor cell hybrids are formed, not DC/tumor cell hybrids.

Spleen cells do not contain proliferating (differentiating) cells, or they are present in a negligible amount. This is consistent with the specification which shows that spleen cells are not a good choice for isolation of DC to make DC/tumor cell fusions. This was not known at the time of the invention which is why the initial experiments were performed (unsuccessfully) using spleen cells. The successful use of other sources such as bone marrow, lymph or blood is shown by the present specification and is the focus of the present claims.

In view of Applicants' submitted Declarations, arguments and amendments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Claims 50-52 and 54-56 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo et al. (1994) in view of Sornasse, et a l. (1992) as applied to claims 1, 4, 5, 6, 7, 9, 10, 11, 15, 16, 17, 18, 20, 21, 22, and 25-29 above and further in view of U.S. Patent No. 5,637,483.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to produce the hybrids by the method of Guo, et al. in view of Sornasse, et al. and employ irradiation before using as taught by the '483 patent. However, since claims 50-52 and 54-56 depend from claim 1, 10, and 21, which are neither taught nor suggested by Guo et al in view of Sornasse, et al. as discussed above, the invention defined in claims 50-52 and 54-56 is also patentably distinguished from the references, alone or in combination. Applicants respectfully request the withdrawal of the rejection.

Claims 13, 14, 23, and 24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo et al. (1994) in view of Sornasse, et al. (1992) as applied to claims 1, 4, 5, 6, 7, 9, 10, 11, 15, 16, 17, 18, 20, 21, 22, and 25-29 above and further in view of Reid, et al.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to produce the hybrids by the method of Guo, et al. in view of Sornasse, et al. and employ the HPRT gene of Reid, et al. However, since claims 13, 14, 23, and 24 depend from claim 10 and 21, which are neither taught nor suggested by Guo et al in view of Sornasse, et al. as discussed above, the invention defined in claims 13, 14, 23, and 24 is also patentably distinguished from the references, alone or in combination. Applicants respectfully request the withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 18-21 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants understand that the claims rejected are claims 13, 23, 35 and 47-49 and assume that the recitation of "Claims 18-21" and also claim 34 are typographical errors.

Claims 13, 23, and 35 are rejected as lacking antecedent basis for "said drug." Antecedent basis for "drug" is found within claims 13, 23 and 35 in the recitation of "drug-sensitive".

Claims 47-49 have been corrected by insertion of a comma.

In view of Applicants' amendments and comments, withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 4-7, 9-18, 20-28, 30-39, and 41-57 are rejected under 35 U.S.C. § 112, first paragraph as the specification does not contain a written description of the claimed invention in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The Office Action states that the original specification and claims do not provide support for reducing the number of tumor cells in a patient in claims 1, 10 and 21 (A); fusion using PEG (B); and "providing an established cell line comprising immortal human tumor cells having at least one tumor-associated antigen in common with said tumor sample" in claim 31 (C).

Support for the reduction in the number of tumor cells in a patient is found in the specification, for example at page 60, paragraphs 1 and 2 which reports that injections of the hybrid cells "prevented the growth of pre-established P815 mastocytoma and provided long term protection." When mice were inoculated with a lethal dose of P815 and subsequently received intraperitoneal injections of hybrid cells, long term tumor protection resulted in 55% of the animals (see Figure 12). In the untreated animals, the tumors grew and killed the animals. The treated mice were also protected against a second tumor challenge (page 60-61, bridging paragraph; Figure 13). More generic descriptive support is found on page 15, paragraph 2, of the present specification which discloses that "the term "activation of immune cells in vivo" refers to the immune rejection of a residual tumor, as measured by its reduction in size and by the survival of the patient, as shown for mice in Example 5C or Example 12.

Support for fusion using PEG is found throughout the Examples. See Example 3 (page 33, line 23), Example 9 (page 46, lines 21-25) and Example 12 (page 54, line 5). Applicants note that the use of PEG to promote cell fusion is well known and is widely used in the art. One of ordinary skill in the art would know that the use of PEG to promote cell fusion is widely applicable to virtually all cell types.

Support for providing an established cell line comprising immortal human tumor cells having at least one tumor-associated antigen in common with said tumor sample is found at page 25, lines 8-12, which teaches that "as an alternative, a pre-established immortal human tumor cell line can be used, provided that at least one of the tumor-associated antigens from the patients' tumor cells are matched to these pre-established immortal tumor cell." See also Embodiments J, K, L, and M at pages 29-30.

In view of Applicants' arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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